

US Biotechnology Small/Mid Cap

KOL call transcript: MPO Inhibitor For ALS & MSA - Verdiperstat Overview

Equities

Americas

Biotechnology

Esther Rajavelu

Analyst

esther.rajavelu@ubs.com

+1-212-713 1461

Jialiang Liang

Associate Analyst

jialiang.liang@ubs.com

+1-212-713 1129

Expert discussion on the role of myeloperoxidase in neurodegeneration

We hosted an investor call with Dr. Frank Tarazi, who serves as an Associate Professor of Neurology at Harvard Medical School and Director of Psychiatric Neuroscience and Clinical Pharmacoeconomics Programs at McLean Hospital, an affiliate of the Massachusetts General Hospital. Dr. Tarazi treats ~30 MSA patients and has basic, translational, and clinical research experience with the role of myeloperoxidase (MPO) in neurodegeneration. See our key takeaway notes [here](#). We include the transcript from our discussion in the following pages.

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We present below highlights from our recent call with Dr. Frank Tarazi, Associate Professor of Neurology at Harvard Medical School and Director of Psychiatric Neuroscience and Clinical Pharmacoeconomics Programs at McLean Hospital. We have edited the transcript below for clarity. Minor grammatical changes that do not impact the meaning of content have been applied. The opinions expressed by Dr. Tarazi herein do not necessarily reflect the views and opinions of UBS. UBS accepts no responsibility for the accuracy, reliability or completeness of the information and will not be liable either directly or indirectly for any loss or damage arising out of the use of this information or any part thereof.

Dr. Tarazi: Yes, I will start, because if they think that it's going to be a little bit of a problem with the connection today.

So, good morning, everyone, and thank you for joining us. I'm Dr. Frank Tarazi. I'm an Associate Professor of Psychiatry and Neurology at Harvard Medical School as well as Clinical Director of private practice, with over 20 years of clinical experience in treatment of mobile disorders, including Parkinson's disease, Huntington disease, and MSA. I also have clinical experience in Alzheimer's disease.

I think the purpose of this talk today is to little bit review MSA multiple atrophy as a disorder, what is the current treatment, and the prevalence and so forth. I think until the moderator joins us, I will start speaking about MSA as a disease that is in great need of new therapies, or to improve over what we already have.

Esther: Hi, Dr. Tarazi, I'm on, but please go ahead.

Dr. Tarazi: I'm just starting by speaking about the disease itself, the clinical presentation, the diagnosis, the disease progression, and the different types that we have.

So, again, from the multiple system atrophy, it does involve more than one system of the brain. It's usually the brain of the body, so, yes, we have abnormalities in the brain, but we also have abnormalities or impairment of functions in other systems.

Typically, the early symptoms of MSA has to do with movement disorders. So, these patients will have difficulty in gait and balance. They will have difficulty in moving, and usually, also, they have frequent falls. They tend to fall quite frequently, even at an early stage of the disease.

The diagnosis of MSA, sometimes it does take time, because some of these symptoms overlap with Parkinson's disease. And therefore, some instance, people will think that this is mostly Parkinson's disease, but then we start noticing that there are impairments in other systems. This can, more or less, start shifting the trend of thinking from diagnosis of Parkinson's disease, perhaps into other disorders, and MSA could be the most option to consider.

There are certain things that can help us to differentiate between MSA and Parkinson's disease. First, MSA, I just want to say it has two types, what we call MSA-P, which P refers to Parkinsonian, and MSA-COVID, which usually refers to cerebella ataxia, where these patients will have abnormalities in the cerebellum causing lack of all coordination, movement, loss of balance, and slow movement.

So, how can we differentiate between MSA and Parkinson's disease? It usually has to do with few symptoms that can guide us in terms of some differential diagnosis between the two disorders. I mentioned about frequent falls. This is something happens in both Parkinson patients and MSA patients, but the frequency, the increased frequency in falls typically happens much earlier in the course of the disease in MSA patients.

Also, there is something, also, very important, what we call dysautonomia, where we start seeing abnormalities or dysfunction of the autonomic nervous system. These patients will have problems with blood pressure, bladder control, stomach emptying, sleep disturbances. Parkinson patients may suffer as well from these symptoms, but they find here that MSA patients will tend to have this dysautonomia much earlier in the

course of their disease.

Then something I'd say is very important to consider, which the symmetry of symptoms is. In Parkinson's disease, the movement disorders tend to happen at one side in the beginning, but in MSA patients, there is more or less symmetric presentations. So, all these movement disorders, or the tremors or rigidity, tend to happen equally or symmetrical on both sides of the body.

Still, it does take time until we properly diagnose MSA. Thankfully, MSA is more rare than Parkinson's disease. In the US, perhaps we have around 800,000 to 1 million Parkinson patients, but we only have around 50,000 MSA patients. The progression of the disease with MSA tends to be much faster than Parkinson's disease. The average life span is between five to eight years after diagnosis. Still remains very difficult to predict what is the progression of the disease, but it's usually much faster than Parkinson's disease, and it varies among patients. Some patients will progress way faster than others.

I said we have two types, the MSA-P and the MSA-COVID. In the US and Europe, the MSA-P, it remains the dominant form, where two-thirds of the patients are considered, or can be diagnosed with MSA-P.

This is just an overall view of MSA as a disorder.

Esther: Okay. You kind of talked about the diagnosis process being difficult. Are there any agents in development, or are there any diagnostic tools in development, that you're aware of, that could potentially improve, or be more specific in identifying MSA patients?

Dr. Tarazi: Well, at this stage, there are some experimental ways to trying to identify more selective biomarkers that can be, more or less, helpful in confirming the diagnosis. Unfortunately, actually, the diagnosis of MSA is confirmed [indiscernible - 51:24]. When we look at the pathology of their brain cells, and we find that we will discuss specific, what we call glial cytoplasmic inclusions, that's what confirms the diagnosis.

In real-life practice, it's mostly what we think it's more probable this is an MSA, or more possible that this is an MSA case. And the reason it does take time, because we have to put the pieces together and show that the involvement of other systems, besides the brain and the abnormality of these patients will experience in terms of movement disorders, to more or less come to a conclusion that this is MSA.

The difficulty here, confirming the diagnosis, the issue, may not change also the treatment outcome, or the prognosis, or the progression of the disease, because none of the treatments that we currently have, or the way we treat MSA patients, is going to make a big difference. We still treat the symptoms as they present themselves. For examples, many of these patients will have hypotension, so we will use agents to increase blood pressure. They will have the movement disorders, we typically use drugs that are commonly prescribed for Parkinson patients, levodopa or dopamine agonists. The problem is, we notice that—and this is one of the ways to confirm diagnosis—that these agents tend to be more effective in Parkinson patients, and way less in MSA patients.

If a patient is given levodopa and dopamine agonist, and we see that the clinical [ph] response is less than typical, or less than what is expected or what is seen in Parkinson patients, this can also tend to tilt the balance in favor the diagnosis of MSA. So, MSA patients tend to poorly respond to the drugs that are commonly used to Parkinson patients.

At this stage, there have been some attempts to further validate or find selective biomarkers, but they are still in experimental stage. Nothing has been close to reach the clinic at this stage.

Esther: Got it. The kind of treatment regimen for MSA then is what, a cocktail of drugs that address symptomatic—

Dr. Tarazi: Yes, we try to relieve the symptoms that they present. So, hypotension, we give drugs to raise blood pressure. Again, for movement disorders or movement symptoms, we give drugs, like mostly levodopa and dopamine agonists, to help [indiscernible - 53:59], bladder control, problems with the GI. But I think one of the most effective still therapies that we have is physical therapy, or behavioral therapies, including physical therapy, occupational therapy, speech therapy, a therapist that will help in eating and breathing. But as you see all these therapists that we have will treat only the symptoms, will not go to the core of the disease. Definitely, they are not disease modifying therapy, and definitely, they will not prevent the progression of the disease.

So, it's more or less of palliative care and treating the symptoms as they present, as much as we can, before, unfortunately, these patients will die from complications of the disease.

Esther: Got it. Can you talk about the neuroinflammatory component in MSA; what causes it, and is there an effective way to manage neuroinflammation in MSA patients?

Dr. Tarazi: Well, neuroinflammation has been proposed as a hypothesis perhaps, or a common ground for a range of progressive neurodegenerative diseases. It's not only been linked to MSA. So, as you see, it's a common ground for many diseases, including MSA, Parkinson's disease, Huntington, ALS, PSP, and others. Even Alzheimer's has been linked to neuroinflammation as well.

Something happens very early in these pathways that's through the cytokines, or it's through interleukin, or through the glial, and these cells will start causing over-activation of neuroinflammatory elements that tend to generate through a cascade of events, what we call oxidative stress, generation of free radicals that eventually will cause a cell and neuronal death. All these progressive disease share a property of a neuronal death, progressive neuronal death.

So, in MSA selective, definitely there is what we call glial cytoplasmic inclusions that are rich with a protein called alpha-synuclein. Alpha-synuclein is a protein found in all cells and in all of us. It's important for cell function, but it is the accumulation of this alpha-synuclein, and the aggregation and dissolving [ph] of this protein, that will start causing problems in the cell by blocking the activity of other proteins, or other enzymes, and by perhaps potentiating oxidative stress generation of free radicals and neuronal death.

Accumulation of alpha-synuclein, again, is not specific for MSA. We have what we call synucleinopathies, where different diseases share this common feature, which is abnormal accumulation or aggregation of alpha-synuclein. Just to give you examples, besides MSA, will be Parkinson's disease, will be Lewy body dementia, and will be PSP, progressive supranuclear palsy.

There are different ways right now in therapies, whether we can try to reduce the expression, prevent them falling, or reduce the aggregation of this toxic protein. Hopefully, this will result in, more or less, closer what we actually need, which is a disease modifying therapy for MSA and other diseases that that share this property.

Esther: Got it. And the alpha-synuclein and the microglial activations, it's similar between MSA-P and MSA-COVID subtypes?

Dr. Tarazi: Yes, to a certain degree, yes. Yes, definitely, to a certain degree. I don't think we have reached a degree to differentiate between the P and the COVID subtypes, but there is some evidence that perhaps this abnormal accumulation of the alpha-synuclein, sometimes there is confirmation, differences in the confirmation of the protein, or the way this protein that aggregates between Parkinson's disease and MSA.

The abnormalities and alpha-synuclein, at this point, is helping us perhaps to differentiate between PD and MSA, and perhaps other diseases that share abnormal accumulation of alpha-synuclein. But, at this stage, MSA-P and COVID are more or less, we think share common, this hallmark of the disease, which is the abnormal accumulation, or the accumulation of the glial cytoplasmic inclusions that we see in postmortem tissue.

Esther: Got it, okay. And so, maybe we can talk a little bit about myeloperoxidase here. What role does myeloperoxidase play in physiological condition, and how does that tie into these neurodegenerative diseases?

Dr. Tarazi: Myeloperoxidase enzyme that are found, also, in different cells, they have, it's like they help, or higher levels of this enzyme can cause microglial activation and neuroinflammation. There is an evidence, at least, that perhaps MSA patients may have this higher activity, or expression of the MPO in microglia.

So, one of the reasons why do we have this microglial activation that can eventually lead to these inclusions, that perhaps, I said before, is this higher activity of the MPO enzyme that triggers a cascade of events through the microglial activation, through neuroinflammation, and then leads to alpha-synuclein. And you see, it's a cascade of events that eventually will lead, at the end, to neuronal death, and the manifestation of symptoms.

So, if we can find if this is overexpression of this activity of this enzyme perhaps by inhibiting the MPO activity, we may eventually try to shut down these cascades of events and prevent the microglial activation, which eventually leads to neuroinflammation, and so forth, along the way.

That's why sometimes these models [ph] have been looked upon potentially as targets for treatments of these diseases that share, again, microglial activation and neuroinflammation as perhaps a common ground. So, this therapy will not be selective. As you know, it's not just being looked upon in MSA. This can also be used or looked upon in other progressive neurodegenerative diseases, including ALS. And I think also Parkinson's would be an example, PSP, Lewy body dementia. All these diseases that share such common pathway in the pathophysiology.

Esther: Got it. But it's the MPO over-activation within the microglial cells that is the underlying pathology here?

Dr. Tarazi: Well, to a certain degree, because we know it is inclusion of the microglial inclusions that are the hallmark of the disease, the glial cytoplasmic inclusions. So, it's a glial inclusion. So, part of the glial cytoplasmic inclusion could result from the neuroinflammation and the microglial activation.

Esther: Understood, okay. Maybe switching gears a little bit to Biohaven's assets here, Verdiperstat, that is now in a Phase 3 trial for MSA. Let's discuss the clinical data that they've shown so far. The Phase 2 trial, which came out a couple of years ago, it enrolled about 51 patients. The high dose showed a lower rate of decline in the UMSARS scores relative to placebo. I think it was something along the lines of 2.6 versus 4.6 over 12 weeks.

Can you help us understand, what's the relevance of that 2.6 score?

Dr. Tarazi: Well, in every trial, you have to have a placebo arm. The typical scale that we use in clinical trials for MSA is the UMSARS, or the unified MSA rating scale. This has different domains that look at the overall functions of the patient, ranging from the motor skills, the skills that specifically, which is going to look at the motor systems; to the autonomic examination, which looks at the dysautonomia, which we said, about the impairment in autonomic functions of different organs, and then the global disability scale.

Now, the trials were done by AstraZeneca, so this is an old drug that has been tried in different trials in Phase 2. None of them actually, there were numerical improvements, this is what they said. I think it did not reach the typical significance, even with the 600 milligrams bid.

Now, if you're telling how much, this is like around two-point separation at such a high dose, no. It did not turn out to be clinically statistically significant when compared to the placebo arm.

At this stage, you only have two points, perhaps it's not, maybe you need a little bit more to achieve clinical significance. But going forwards, I think the dose that will be used is 300 milligrams bid in the ongoing Phase 3 trial. And 300 milligrams even was weaker than 600 milligrams bid, so we're talking about 0.9 in point separation from placebo, which I think is still clinically insignificant.

The only big difference between the Phase 2 trial and the Phase 3 trial is the duration. The Phase 2 trial was only for 12 weeks, now we have the 48 weeks. Perhaps these agents that will try to prevent neuroinflammation and prevent microglial activation do need a long, and eventually shut down these cascade of events that will eventually lead into less neuronal deaths and improvement of symptoms, may need longer than 12 weeks to achieve this clinical improvement.

So, we will see. The trade-off here, you have the lowered the dose. Perhaps going for 48 weeks with a dose that has shown more benefit, but only for 12 weeks, may also start causing adverse events or side effects. So, the idea is to go perhaps with the lower dose, as they are doing right now, 300 milligrams bid, but for a much longer duration, 4 times instead of 12 weeks, we're going all the way for 48 weeks.

Esther: Got it. But just in terms of the scale that's being used, can you maybe just give us an idea of when you diagnose a patient, are you using this scale? For your current MSA patients, what kind of decline do you see in that scale over the course of a year, or whatever method you use?

Dr. Tarazi: Yes, I think, as I said, many times these scales, it will help us to guide us. Most of these scales are used actually more in details in clinical trials, and less in clinical practice, but these help us to establish a baseline, and then determine, as we go along, about the progression of the symptoms, and how is this patient doing afterwards, because we tend just to compare the background or the baseline as we go along with the different symptoms.

Now, in terms of points, you will see, it's very difficult, I can tell you, to predict the progression of the disease in different patients. So, it's not like during the first year you have like three points loss, or five points loss, so forth. It varies a lot. The variability is so high in MSA, and that's one of the things sometimes can cause problems in clinical trials, where you have to enroll perhaps more patients to reduce the variability, and the standard deviation that we typically see among patients.

Yes, I said that the progression, or the course or the journey of the disease, could last between five to eight years after diagnosis, but in some patients we have seen that they have live much longer, 12 years or longer, after diagnosis. So, there is a tremendous variability, and we have to deal with each patient, there's no clear set rate of the degeneration or progression that usually fits all.

Esther: Got it, okay. Maybe kind of looking, again, at that same dataset, the Phase 2 dataset, and the PET scans that were intended to show microglial activity. Why do you think the PET scans failed to show change of microglial activity in the MSA patients in the Phase 2?

Dr. Tarazi: Well, you're talking about the post [ph] PET scan?

Esther: Yes, the TSPO PET scans.

Dr. Tarazi: Yes, the TSPO. This is a nonselective biomarker, or a nonselective scan for neuronal activations. It's not something that is widely used in clinical practice, and tends to be, I think, in much earlier stage, because it does look at the selectivity of this PET scan, and how useful it is, and what kind of information we are going to get out of it. It is a nonselective biomarker for neuroinflammation, and it can be used across different neurodegenerative diseases.

The microglial activation and neuroinflammation, those are much earlier in the phase of the disease, or before even the symptoms start to show up, and, as I said, they trigger a cascade of events that eventually lead to the development of symptoms. They are nonselective, so have been proposed that as a biomarker, but I'm not sure how selective

and how sensitive it is to the symptom itself.

And then there is something very important. We don't have any correlation between the changes in biomarker and the development of the symptoms, or the severity of the symptoms, and even in terms of predicting the progression of the disease.

So, the TSPO PET scans right now have been suggested as potentially that can be useful more in clinical trials, but I think it's a long way before this can be adopted in clinical practice as a valuable, and a valid and selective biomarker to help us predict the diagnosis, or confirm the diagnosis and predict the progression.

Esther: Got it, okay. So, the fact that it didn't show any changes in microglial activity probably, to you, means that the patients were already symptomatic, so there was nothing much can be imaged?

Dr. Tarazi: Yes, maybe, at that stage, the microglial activation is not as prominent, in terms of developing symptoms. At this stage, again, we treat patients when symptoms show up. I'm speaking about the behavioral symptoms. This microglial activation and neuroinflammation usually happen much earlier before the symptoms of a disease show up, not just MSA, other diseases.

So, it will be very difficult to be able to find these patients, unless there is a genetic reason, or a familial reason, but typically, it will be very difficult to screen at the much earlier stage, in the asymptomatic stage. In fact, it does take even years, in some instances, before confirming the diagnosis, even after the behavioral symptoms show up.

Esther: Understood, okay. Maybe can you talk about MPO in the peripheral and systemic functions, and how does that differ from the CNS?

Dr. Tarazi: Again, it is potentially found in the periphery. We want to see not in—usually the activity of enzymes tends to carry higher degree of risk, and potentially side effects, because these enzymes are found everywhere, and you may perhaps block the activity of the higher activity or the activation of the higher activity of this environment, the brain. Since these drugs are going to be given oral, not, say, intracranial, then it may have side effects in the periphery by blocking the activity of the MPO in peripheral organs.

But I think, at this stage, safety, it's very important, but I think if this drug is successful down the road, it's going to be more effective towards the motor symptoms, and way less towards the autonomic dysfunction that we see. Because even in the ongoing primer and point that they are using, they are focusing on the UMSARS part one and two, and one is the historical review of the nature of the disease, and the other one, part two, or domain two, is for the motor symptoms. They have not included the domain three, which looks at the autonomic functions. If this will be successful, definitely it'll be more useful towards the motor impairment that we see in the disease.

But in a disease where we have actually minimal or no effective treatment, even if this will show benefit towards a subset of symptoms, definitely this will be of significant clinical value.

Esther: Got it. So, in your view, MPO inhibition in the plasma, are there any specific side effects that you would be concerning?

Dr. Tarazi: Well, it's difficult specifically to say, but that's why an extensive review of all adverse events is needed in trials of this kind. Also, remember, these patients do have autonomic dysfunction, so are they going to worsen the autonomic dysfunctions that these patients suffer from?

It's very important to say because it's an MSA, it's not only the brain that is involved, and other peripheral systems and organs are also involved. So, it is important to see that this drug, if it improves the symptoms of the brain, or the movement disorders, it does not worsen the peripheral symptoms, or worsen the autonomic dysfunction that already these patients are suffering from.

Esther: Got it. But from your perspective, I mean, the motor function is sort of the key symptom that's not addressed by the agents that you have at your disposal to manage these patients?

Dr. Tarazi: Well, all the agents that we have, to a certain degree, provide palliative care more than effective or therapy. The dysfunction of the autonomic system, nervous system, is also a crucial part of the MSA. In fact, we think upon diagnosis, those patients, we have noticed, that have more severe autonomic dysfunction upon diagnosis, tend to progress worse than others, and the survival rate tends to be shorter.

It is important to have therapy that, at the end, will address all core symptoms of the disease. Until we reach this, then definitely, if this drug appears to be more effective towards the motor symptoms, as I said, this will be a valuable addition to the treatment.

Esther: Understood, okay. In the ongoing Phase 3 trial, I guess you kind of talked about the UMSARS part one versus part two, and you've also talked about the 48 week versus 12 weeks of changes, relative to the Phase 2. I guess the question is, 48 weeks is almost a year, in the natural history of the disease, can you give us some sort of metric on, in your experience at least, like how much patients progress on the UMSARS scale?

Dr. Tarazi: Well, in terms of points, again, I can't tell you it all is the same. I've seen patients who will progress two, three points, and patients who will progress seven or eight or ten points. So, it varies a lot. Really, it has to boil down individually. The progression has been proven very difficult, and as I said, the standard deviation, when we do trials, seem to be very big, which are the huge variability among the progression or the survival rate.

The mean of five to eight years is just a mean. There will be patients less, and definitely patients way more than that. But a year, for 48 weeks, because most of the time they are trying to also recruit patients that are early in the course of the disease. That's important. So, patients that they think upon diagnosis that they're still in the milder phase, so these patients still can be independent. They don't have to have ambulatory service, or people well taken care of every day on a daily basis. They also propose that they have at least profits [ph] of three years or longer, in terms of their survival.

They are trying to have patients in an earlier course of the disease, and I think I agree, because now we know, with progressive neurodegenerative diseases, the earlier we intervene, the better will be the outcome. Because as it is progressive, they would reach a point of what I call of no return, where any therapy, whether immunotherapies, or small molecules, or inhibitors of enzymes, will be less effective than when intervened earlier.

Esther: Understood. And in terms of, the trial, obviously, is enrolling both MSA-P and MSA-COVID patients, and the analysis, they're grouping both subgroups together for the analysis. What is your thought on that, from an analytical standpoint?

Dr. Tarazi: First, again, as I said, two-thirds of the cases in the US are typically MSA-P. Interestingly, in Japan, there are some studies suggest that MSA-COVID is the more dominant form. But it's good first to look at an overall MSA, but then look at the subtypes, because sometimes we do this with other trials, where we have either subtypes, or sometimes specific carriers like, I'll tell you, for Alzheimer's disease, sometimes they do genotyping based on the APOE4 carriers and non-carriers.

So, it will help them to understand, overall, the impression, or the outcome, or the benefit of the drug on the overall population of patients. But maybe as they do the division of groups and subtypes, that the drug can or maybe will be more effective towards, say, MSA-P versus MSA-COVID, and vice versa. So, even identifying a subtype of the disease will still be useful. Remember, we are dealing with a disease that actually has not effective treatment, so if we can even, like if this drug, let's say, theoretically, turned out to be more effective for one form or one type over the other, still this is valuable.

I think what they're doing is correct, in terms of assessing the overall population of patients that they are enrolling, then specifically trying to find whether there are differences in the response of patients to this drug based on the type of the disease

they're carrying.

Esther: Got it. Do you know if these patients are being treated with other agents for systemic management?

Dr. Tarazi: Well, I'm sure that these patients will be getting medication for the autonomic dysfunction, and that's, I think, important, yes. But remember, because these patients will still experience bladder problems, and they will still experience GI problems, and sleep, so I think these other symptoms still need to be managed. And remember, the autonomic dysfunctions are not part of the endpoints of the trial.

As long as you also have the placebo, you want to make sure that those placebo controlled randomization, that these patients are equally randomized across placebo and drug treated arms, and this will correct for any potential medications they are on to treat the other symptoms.

Esther: Got it, okay. So, I'm going to pause there and see if any one of our listeners has anything on MSA that they want to ask, otherwise I'm going to move on to ALS in the remaining time.

Operator, do you want to pull for questions?

Coordinator: Thank you. I actually have a question here on email. The listener wants to know, in terms of other agents in development for MSA, how confident do you feel about myeloperoxidase inhibition versus other mechanisms?

Dr. Tarazi: Yes, it is a mechanism that's perhaps worth exploring. I can tell you, MSA is a difficult disease to treat, and one of the reasons because it involves multiple systems. It's also highly progressive, compared to Parkinson's or compared to Alzheimer's. And also, because it's relatively rare compared to other diseases, like Parkinson and Alzheimer's.

It's definitely a mechanism that's worth exploring. Though, it does tend to carry a high risk, but what we call high-risk high-reward approach. How selective the inhibition of the microglial activation that will eventually lead to improvement of symptoms, we have seen from Phase 2 the results were not extremely outstanding. There were some numerical improvements, but again, that favor perhaps this approach, or this target, but now, the ongoing trial really will validate the drug as an effective treatment. And I think it also will validate the pathway and the target that they are going after, whether it is of value or not. Because if a drug, let's say, after 48 weeks, we don't see significant clinical improvement, it is unlikely that we are going to see an effect longer than this.

I think that's the answer to your question, will be really the results of the ongoing trial. The results will tell us whether this is a valid target, whether this is an effective drug, based on the inclusion criteria, based, also, on the duration of the trial.

Esther: Understood. Operator, anything else on the line, in the queue?

Coordinator: There are no current questions on the audio.

Esther: Perfect. Let's move on to ALS. Do you have insights into the HEALEY ALS Platform Trial that's managed by Mass General?

Dr. Tarazi: Yes, of course. It's a new platform right now that is involving different aspects; academia, FDA, hospitals, pharma companies, all coming together, under one umbrella and one platform, to try to facilitate and speed up the process of developing their new drugs and executing new drugs for ALS. I think it's a valuable platform, in a centralized way, that helps us to expedite the conducting trials.

Because, also, ALS is another rare disorder with a high degree of progression, I think even the lifespan of patients with ALS is even shorter than MSA. We're talking about typical two to three years in some instances, five years. So, most of the patient's survival after diagnosis will tend to be two to three years.

It's a very valuable, again, platform that includes different stakeholders or players in the field, which will eventually, we hope, will result in faster development of drugs for ALS.

Esther: Got it. So, there are three drug candidates, as I understand, and Verdiperstat and being one of them in that program. How were these drug candidates selected?

Dr. Tarazi: It's based on perhaps the steering committee, and some preliminary data that has some of these compounds already have been tested in other diseases, or have had a Phase 2 trial data that appears to be supportive of the concept of neuroinflammation or neuroprotection. Again, many of these drugs that you look at them, they share common platform, in terms of trying to inhibit neuroinflammation, and trying to inhibit neuronal death by providing some of a neuroprotective growth through different mechanisms of different approaches.

One of the drugs has been already tested before in Huntington's disease. The Biohaven drug, Verdiperstat, is already tested in MSA. As I said, there are some cues, or clinical data, or evidence of support to include in these trials, but again, to a certain degree, they do carry high risk, in terms of never been tested in ALS, and it's a very difficult disease to treat, also. But definitely, that's part of the clinical research and clinical development of new drugs.

Esther: Got it. Can you help us understand the primary endpoint of that trial, which has the revised ALS function—

Dr. Tarazi: Yes, yes, yes. As we have the UMSARS, the unified MSA rating scale, also, with ALS, we have what we call the ALS function of rating scale, which the ALS FRS. So, this used to consist of ten items that will look at different functions of the patients, anything from speech, to swallowing, to handwriting, to walking, climbing stairs, and breathing.

Functional activity, or breathing problem, or a respiratory problem are very prominent in ALS, and unfortunately, many of the patients eventually will die from pulmonary failure. The revised scale, it was expanded from ten items to 12 items, and they included 2 new items. One is called orthopnea and one is called respiratory insufficiency. These two items were added to more extensively evaluate the respiratory functions of the patients.

Orthopnea is basically shortness of breath, and for problems, difficulty with breathing, especially when a patient is lying down. Respiratory insufficiency is just the lungs are unable to fully have, in terms of taking oxygen and expelling carbon dioxide.

So, that's the thing. They added two more items specifically to further evaluate the respiratory functions of patients. It is the most common widely used endpoint that has been used in clinical trials across different drugs.

Esther: Got it. As you indicate, ALS has a busy pipeline with several agents in development. What is your view on Verdiperstat relative to the other agents in development? Do you see this as a disease modifying potential, or compared to some of the other agents that are in the pipe?

Dr. Tarazi: Well, there is not much, again, for ALS. We only have two drugs approved for ALS at this stage, Riluzole and Radicava. There has been some interesting data coming out with a new drug called AMX0035.

And so, again, because we know it's a progressive neurodegenerative disease that neurons die very rapidly and very quickly, we always are trying to find ways to prevent this neuroinflammation that can cause this neuronal death, or come out with drugs, what we call neuroprotective or neuroprotection, to prevent the death of neurons.

The four or five drugs, the five drugs selected by this platform, they all share this goal, but they are coming through different pathways or different approaches. One is using the MPO inhibitor; one is targeting the Sigma-1 receptor, or a partial agonist of the dopamine; one going through immunotherapy, targeting the CD14.

So, it's different approaches, but eventually, their main goal is to hopefully prevent neuroinflammation, protect the neurons from dying, and hopefully disease modifying, yes. This is what we are hoping for. This could be disease modifying if it results in less neuronal death, and slowing down the progression of the disease, and, of course, increasing survival rate.

Esther: Understood, okay. And in terms of, where do you think Verdiperstat has a higher likelihood of success, MSA or ALS, and what are some considerations as we think about both of those programs?

Dr. Tarazi: Well, at this stage, both are major unmet need, both are highly progressive disease. There is a great unmet need because we have basically no effective treatment. So, I think it's worse than any of these diseases. Of course, in both will be great expectations, but even if it hits in one, will be of significant value, because there is a great need for new treatments in both diseases.

At this stage, which one I think will work, it will difficult to predict, again, because Verdiperstat is used towards motor symptoms, and I think towards the inhibiting neuroinflammation, which tend to be more useful to a subset of symptoms than MSA. But in ALS, though, they do have respiratory abnormalities and impairment. It will be, again, both drugs are going to be high risk, no doubt, because that's one of the reasons we don't have effective treatment, because we have tried things in the past that were not effective enough. But they carry high risk, but they also carry high reward, and they are going to fill a major unmet need.

Esther: Got it. But the rate of progression between ALS versus MSA, you said ALS, the patients progress a lot faster, you don't think that has any potential, for success in one versus the other?

Dr. Tarazi: Well, we have to wait and see in these clinical trials. Both have a high risk of failure as well, high-risk high-reward, in terms of achieving significant benefit. That's the problem with these procedures. That's why we don't have enough treatments. But ALS definitely progresses faster, the average two to three years. Here, we're talking five to eight, but we've seen patients that have lived 12 years or longer with MSA. Again, the impairment of the autonomic nervous system appears to contribute a lot to the severity of symptoms and the longevity of patients.

Esther: Got it. In terms of diagnosing ALS, you don't have those similar challenges that you have with MSA, do you?

Dr. Tarazi: Yes, to a certain degree, yes, a certain degree. I think, also, the tests that we use, yes, because it's mostly a brain disorder, ALS, and then the other ones, as it progresses. But here, we have multiple systems, from the name, multiple system atrophy, which makes it more difficult to manage all these symptoms and provide effective treatment.

But the diagnosis of ALS also sometimes comes very quickly. And because of the progression of the disease, by the time, unfortunately, these patients are diagnosed, the disease has progressed significantly.

Esther: Got it, okay. I'm going to open up the call again for any other last questions that we have for Dr. Frank Tarazi. Operator, if you want to open the poll again.

In the meantime, Doctor, you've been sort of treating these patients, and dealing with the payer environment as well, so do you have any comments on that front, in terms of the current therapies that are being used, and how receptive are payers to these drugs?

Dr. Tarazi: Yes, again, for MSA, we don't have any specific therapy. All the drugs that we use are generic, whether for hypotension, or whether for bladder control. They're cheap and available, so there is no issue, because these drugs are not being developed or approved for MSA. These are just drugs approved for other indications that we use in these patients. All these drugs are available in generic form.

The only drug that is expensive with ALS is Radicava, because it does require IV administration and infusions, and so forth. That's an expensive one, but we haven't had real issues in terms of payer coverage.

I think because of the major unmet need, if any of these drugs will show benefit and are approved, whether for MSA or with ALS, definitely will be of value, and I don't think they will find enough resistance from insurance companies to cover, even if they are expensive, based on the unmet need, and really the need to help these patients and their families.

Esther: Got it. Is there any reason to think that it would work in one and not the other? And if that's the case, do you anticipate sort of off-label usage across the indications?

Dr. Tarazi: Well, if the drug is approved, then perhaps it could be, but let's wait across the space. We have to show benefit, enough clinical benefit in one disease. There is also high probability that it may not work in any, unfortunately. It will be a disappointed outcome, but it won't be totally surprising, based on the multiple failures we had in the past with trials for these two diseases.

But if it's approved and it's on the market, and it does show enough clinical benefit, at least in improving the motor symptoms, and it's specific disease, whether ALS or MSA, then potentially this could be used off-label, but that's not something that is any time soon. We do need to have enough clinical experience with any of these medications prior to, say, using it off-label in other diseases.

Esther: Got it. To that question then, assuming it does get approved in MSA, do you sort of see a bolus of patients, and do you kind of expect really quick uptake within your clinic, or do you think of this as sort of gradually gaining experience and adding use?

Dr. Tarazi: Well, like any drug, when it comes to the market, it's more or less will depend on the personal experience and the response of patients, and also feedback from peers. Remember, clinical trials are always a close setting that depends on the patients who are enrolled in that specific trial, and inclusion criteria, in many instances, tend to be very small, versus the exclusion criteria, which tend to eliminate number of conditions, either comorbid conditions, or can more or less intervene with the outcome of the trial. This cannot happen in real-life practice.

Any drug that comes, we'll have personal experience with, and as we get, say, positive feedback from patients, what we see in terms of personal experience, and also feedback from peers and colleagues, then they may very well tend to grow the market growth, because of the unmet need. There are no alternatives to compare to. So, if this drug gets the FDA approval for MSA, definitely this will be of value.

I think if the outcome or the feedback comes positive, then definitely there will be room and place for this drug to grow.

Esther: Awesome. Well, I think that's all I have. I want to thank you for your time. Operator, if there are any questions, feel free to queue those up, otherwise, we will thank the doctor for his time, and look forward to staying connected.

Coordinator: Thank you. There are no current questions on the audio.

Esther: Well, thank you, Dr. Tarazi, for your time. I really appreciate all the information you've shared.

Dr. Tarazi: Thank you. Thank you, everyone. Stay safe and take care. Bye-bye.

Coordinator: Thank you to all speakers. That concludes your conference call for today. You may now disconnect. Thank you for joining, and enjoy the rest of your day.

[END OF CALL]

Valuation Method and Risk Statement

Key risks include negative clinical trial data, delayed trial enrollment, adverse regulatory rulings, and pricing and competitive launch dynamics.

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Buy	Stock price expected to rise within three months from the time the rating was assigned because of a specific catalyst or event.	<1%	<1%
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UBS Securities LLC: Esther Rajavelu, Jialiang Liang.

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Company Name	Reuters	12-month rating	Price	Price date
Biohaven Pharmaceutical Holding Co Ltd ^{16,20}	BHVN.N	Buy (CBE)	US\$64.07	29 Mar 2021

Source: UBS. All prices as of local market close.

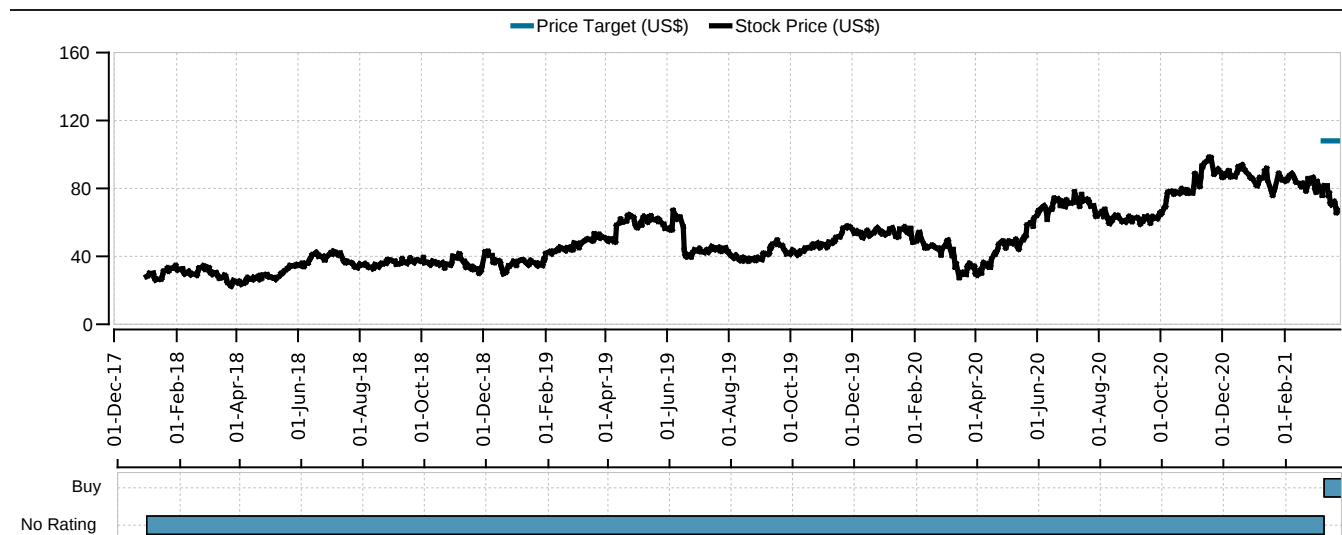
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Biohaven Pharmaceutical Holding Co Ltd (US\$)



Date	Stock Price (US\$)	Price Target (US\$)	Rating
2017-12-29	26.98	-	No Rating
2021-03-10	75.94	108.00	Buy

Source: UBS; as of 29-Mar-2021

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